

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ :	A1	(11) International Publication Number: WO 95/22320 (43) International Publication Date: 24 August 1995 (24.08.95)
(21) International Application Number:	PCT/US95/01928	(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UG, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).
(22) International Filing Date:	17 February 1995 (17.02.95)	
(30) Priority Data:	08/200,045 22 February 1994 (22.02.94) US	
(71) Applicant:	GLAXO WELLCOME INC. [US/US]; Five Moore Drive, Research Triangle Park, NC 27709 (US).	Published <i>With international search report.</i>
(72) Inventors:	COFFIN, Mark, Davis; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). PARR, Alan, Frank; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US).	
(74) Agents:	JOYNER, Charles, T. et al.; Glaxo Inc., 5 Moore Drive, Research Triangle Park, NC 27709 (US).	

(54) Title: RANITIDINE SOLID DOSAGE FORM

(57) Abstract

The present invention comprises a bilayer, pharmaceutical tablet having one layer formulated for the immediate release (IR) of ranitidine and a second layer formulated for sustained release (SR) of ranitidine with the ratio of ranitidine in the IR layer to that in the SR in the range of from about 30:70 to about 60:40.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LJ	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

RANITIDINE SOLID DOSAGE FORM

The present invention relates to pharmaceutical solid dosage forms having an immediate release layer and a slow release layer with each layer containing
5 ranitidine as an active ingredient:

BACKGROUND OF THE INVENTION

The drug ranitidine, chemically identified as N-[2-[[[5-(dimethylamino)methyl-2-furanylmethyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine and its physiologically acceptable salts are described and claimed in US Patent 4,128,658, and a particular crystalline form of ranitidine hydrochloride is described and claimed in US. Patent 4,521,431 (both incorporated herein by reference). In both these patents there is reference to formulations for oral administration, which may, for example, be in the form of tablets, capsules, granules, powders, solution, syrups, suspensions, or tablets or lozenges for buccal administration. Oral preparations of ranitidine are also disclosed in US. Patents 4,585,790, 4,880,636, 5,028,432, 5,068,249 and 5,102,665. As used herein, the term "ranitidine" refers to both the free base and the pharmaceutically acceptable acid addition salts thereof unless otherwise noted.

Ranitidine is an antagonist to histamine H₂ receptors. This drug is widely used in the treatment of duodenal ulcers in humans in the form of the hydrochloride salt. While the drug is generally given orally or by injection, the oral route is preferred. Ranitidine HCl is sold under the trademark Zantac® by Glaxo Inc. of Research Triangle Park, North Carolina.

Recently ranitidine has been approved by the FDA for treatment of esophagitis. The patient suffering with esophagitis is effectively treated by administration of 150 mg of ranitidine four times a day. However, the four times a day dosing regime often leads to poor patient compliance. Studies have shown that patient compliance increases as the dosing regime goes from four times a day to twice or once a day. Therefore, a dosage form that reduces the ranitidine daily dosing regime, while maintaining a stable plasma level of ranitidine, i.e., a sustained release form, would be advantageous.

Clinically acceptable sustained release forms of ranitidine using conventional technology have not heretofore been successful. Ranitidine has

50% absolute bioavailability, and it is only absorbed in the initial part of the small intestine. These properties are not favorable for sustained release delivery means.

5 Numerous patents teach a sustained drug release system and list ranitidine as a suitable candidate. However, such systems do not allow for the peculiar properties of ranitidine and thus yield less than ideal sustained release formulations. That is, these systems do not allow for the balance that must be made between the amount of the drug immediately released and the amount of
10 time over which the remaining drug in the sustained release (SR) portion is released. For example, if too much ranitidine is present in the immediate release (IR) portion, the result is essentially the same as that obtained with the commercially available tablets, i.e., an immediate release formulation. Conversely, if too little ranitidine is present in the immediate release portion, the
15 resulting formulation exhibits poor bioavailability.

20 Multilayer, solid drug formulations have been known in the pharmaceutical art for several years. These formulations usually consisted of coated tablets and pellets or multiple-layer tablets (either bi- or tri-layer tablets). Usually the layers are "built up" with multiple coatings on a tablet core, a process widely practiced in this art. Examples of the application of multilayer drug formulation to improve the *in vivo* activity of a drug are given by Kim, et. al. (US. Patent 4534973) and Leslie, S. T., et. al. (*Pharmaceutica* 2(3), pp.192-194, 1979). The use of multilayer drug formulations (either as multiple-layer tablets or coated tablets or pellets)
25 have been used to sustain the blood level of various drugs. Examples of these types of systems have been applied to theophylline, phenylpropanolamine, aspirin, and many others. In practically all cases, this approach has been applied to drugs that are well absorbed and drugs that are absorbed throughout the entire gastrointestinal tract.

30

SUMMARY OF THE INVENTION

35 The present invention comprises a pharmaceutical solid dosage form having a first layer with an immediate release property and a second layer with a sustained release property. Each of these layers contains ranitidine, with the ratio of the ranitidine in the first layer to the ranitidine in the second layer being in the range of from about 30:70 to about 60:40 by weight.

Another aspect of the present invention is a method of treatment comprising administering to a patient in need thereof a pharmaceutical solid dosage form of the present invention wherein the total amount of ranitidine is a pharmacologically effective amount.

5

DETAILED DESCRIPTION OF THE INVENTION

The solid dosage form of the present invention features a balance between immediate release and sustained release of ranitidine which provides a significantly more uniform, efficient delivery of ranitidine than oral formulations of ranitidine now available on the market. This dosage form may be used for the same indications as the ranitidine tablets now in clinical use. However, it is especially useful where it is desirable to maintain a sustained, uniform dose of ranitidine for twelve to twenty-four hours with the administration of only one or two doses.

In particular, the solid dosage form of the present invention may be in the form of a compressed tablet having at least one layer containing ranitidine formulated for immediate release and at least one layer containing ranitidine formulated for sustained release. The layers may be concentric, laminated in a tablet or in mini tablets, or beads to be administered in a capsule. Conveniently, the present invention may be in the form of a bilayer tablet.

Ranitidine may be used in the dosage form of the present invention in a total amount of from about 25 to about 800 mg per unit dose, calculated as ranitidine base. In particular, a unit dose of about 100 to about 350 mg, e.g., 150 mg (168 mg as the HCl salt) and 300 mg (336 mg as the HCl salt) may be used.

By employing the oral, solid ranitidine dosage form taught herein, a patient suffering with esophagitis, at the discretion of the attending physician, may be treated only once or twice a day rather than four or more times a day with conventional oral dosage forms of ranitidine. The less frequent need for dosing is more convenient and easier for a patient to remember to administer. Thus, dosing compliance is higher than with conventional oral forms of ranitidine.

35

Ranitidine hydrochloride can be prepared in two crystalline forms, i.e., Form 1 disclosed in US. Patent 4,128,658 and Form 2 disclosed in US Patent

4,521,431. While either Form 1, or Form 2, or any other form may be used in the present invention, Form 2 is preferred.

As used herein the term "immediate release" or "IR" means a dosage form
5 that delivers the entirety of its drug content at once after administration for the purpose of providing a rapid rise and fall of drug concentration in the blood stream. The term "sustained release" or "SR" means a dosage form that gradually releases its drug content over a given period of time after administration for the purpose of providing a constant concentration of drug in the blood stream. The
10 term "active ingredient" means a drug, e.g., ranitidine. The terms "excipient" or "inactive ingredient" means material added to a solid pharmaceutical formulation to impart certain desirable properties. For example, in the case of a tablet, excipients may be added to moderate dissolution rate, mask a bad taste, or improve appearance of the tablet. The term "matrix" or "matrix system" means the
15 combination of all excipients of a given formulation in which the active drug is incorporated.

In the present invention, in addition to ranitidine, other active ingredients, e.g., other H₂ antagonists, antacids and synergizing agents, may be added to the
20 formulations of either or both the IR and SR portions of the solid formulations, e.g., to the IR and SR layers of a tablet. Likewise, excipients such as binding, matrixing, disintegrating, sweetening, coloring, antioxidantizing, protecting and lubricating agents may be added to the formulations of either or both the IR and SR portions, e.g., layers of a tablet. Further, the layers containing active
25 ingredients, separate or in combination, may be overcoated with one or more layers of excipients. For example, a tablet containing an IR and SR layer fused together may be overcoated with a layer containing a coloring, antioxidantizing and protecting layer.

30 In particular, the IR layer comprises ranitidine, filler such as lactose, matrix agents such as microcrystalline cellulose and croscarmellose sodium, a lubricant such as magnesium stearate, and optionally other excipients and other active ingredients.

35 In particular, the SR layer comprises ranitidine, a matrixing agent such as hydroxypropyl-methylcellulose, filler such as lactose, a lubricant such as magnesium stearate, and optionally other excipients and other active ingredients.

A particular embodiment of the present invention is a pharmaceutical solid dosage form, e.g., a bilayer tablet, comprising:

1) An IR layer containing ranitidine together with:

	<u>Ingredient</u>	<u>Ratio to ranitidine (by weight)</u>	
		<u>from about</u>	<u>to about</u>
	a) microcrystalline cellulose	1 : 0.6	1 : 3.3
	b) croscarmellose sodium	1: 10	1 : 200
	c) magnesium stearate	1:25	1:400
10	d) other optional excipients and/or active ingredients ¹	-----	-----

2) An SR layer containing ranitidine together with:

	<u>Ingredient</u>	<u>Ratio to ranitidine</u>	
		<u>from about</u>	<u>to about</u>
	a) hydroxypropylmethyl-cellulose	1:0.1	1:1.3
	b) lactose	1 : 0.3	1 : 2
	c) magnesium stearate	1: 12.5	1: 100
20	d) other optional excipients and/or active ingredients ¹	-----	-----

¹The ratio of the other excipients to ranitidine in each layer will vary according to the nature of each excipient, but would be in the range of from about 1:1 to about 1:500 by weight. Likewise, the ratio of other active ingredients will vary according to the nature of each active ingredient, but would be in the range of from about 100:1 to about 1:100.

30 wherein the ratio of ranitidine in the IR layer to ranitidine in the SR layer is in the range of from about 30:70 to about 60:40 by weight. In particular, this ratio is the range of from about 35:65 to about 55:45.

35 A more particular embodiment of the present invention is a bilayer tablet comprising,

1) an IR layer containing

a) about 50 to about 200 mg of a ranitidine acid addition salt,

- b) about 60 to about 90 mg of microcrystalline cellulose,
- c) about 1 to about 5 mg of croscarmellose sodium,
- d) about 0.5 to about 2.0 mg of magnesium stearate and
- e) optionally other excipients and/or other active ingredient

5 and

- 2) an SR layer containing
 - a) about 50 to about 200 mg of a ranitidine acid addition salt;
 - b) about 150 to about 350 mg of hydroxypropylmethylcellulose,
 - c) about 100 to about 150 mg of lactose,
 - d) about 2.0 to about 4.0 mg of magnesium stearate and
 - e) optionally other excipients and/or other active ingredients.

Specifically, in each layer ranitidine is in the form of its hydrochloride salt.

15 The ratio of the amount of ranitidine hydrochloride (calculated on the basis of the free base) in the IR layer to that in the SR layer is in the range of from about 30:70 to about 55:45 by weight. Particularly, the ratio of ranitidine hydrochloride in the IR layer to that in the SR layer is in the range of from about 40:60 to about 55:45. For example, this ratio may be 40:60 to 50:50.

20 The rate of release of ranitidine from a matrix, i.e., the dissolution profile, is controlled by the rate of diffusion of ranitidine through the matrix. Changes in tablet shape which affect tablet surface area may change the dissolution profile. Thus, one skilled in this art will appreciate that a change in tablet shape may 25 cause a change in surface area which may require some adjustment of the IR:SR ratio to produce the optimum, desired dissolution profile.

30 The sustained release layer of the pharmaceutical solid dosage form of the present invention delivers its ranitidine content over a four- to ten-hour period at a nearly constant or zero-order rate. In particular, it delivers ranitidine over a six-hour period at a nearly constant or zero-order rate.

35 The pharmaceutical solid dosage form of this invention may be prepared according to procedures known in the art of pharmacy for preparing multilayer dosage forms (see Gunsel W. C. and Dusel R. G., "Compression-Coated and Layer Tablets," In Lieberman, H. A.; Lachman, L.; and Schwartz, J. B. (eds.), *Pharmaceutical Dosage Forms: Tablets*, Vol. 1, Marcel Dekker, pp. 247-284 Inc., New York, 1989). Conveniently, to make a bilayer tablet, blends for the

immediate release and sustained release layer are prepared separately. Each blend is then loaded onto a layer press and compressed using standard procedures well known in the art.

5

EXAMPLES

The following examples illustrate aspects of this invention but should not be construed as limitations. The symbols and conventions used in these examples are consistent with those used in the contemporary pharmacy literature, 10 for example, *Pharmaceutical Research*.

As used herein, the terms "300 mg" and "150 mg" mean the tablet formulation contains 300 mg and 150 mg, respectively, of ranitidine calculated as the free base. Avicel brand of microcrystalline cellulose and Ac-Di-Sol brand of 15 croscarmellose sodium, both supplied by FMC Corporation, 1735 Market Street, Philadelphia, PA.19103, were used in the following examples.

20

EXAMPLE 1

"300 mg" Tablet formulation with the IR:SR ratio of 50:50

Ingredient	Amt/tablet
Immediate release layer	
Ranitidine HCl	168.0 mg
Microcrystalline cellulose	78.3 mg
Croscarmellose sodium	2.5 mg
Magnesium stearate	1.2 mg
Sustained release layer	
Ranitidine HCl	168.0 mg
Hydroxypropyl methylcellulose	300.0 mg
Lactose	129.0 mg
Magnesium Stearate	3.0 mg
TOTAL WEIGHT	850.0 mg

Sieving of materials:

A sufficient quantity of the materials are sieved through the listed screen:

	<u>Ingredient</u>	<u>Screen Size Range</u>
	Ranitidine hydrochloride	14 - 40 mesh
	Hydroxypropyl methylcellulose	20 - 60 mesh
5	Microcrystalline cellulose	20 - 60 mesh
	Lactose (monohydrate)	14 - 40 mesh
	Croscarmellose sodium	14 - 40 mesh
	Magnesium stearate	40 - 60 mesh

10 Powder Mixing

Sustained Release Layer

15 The ranitidine hydrochloride, lactose (monohydrate) and Hydroxypropyl methylcellulose are added to a suitable mixer (*i.e.*, twin shell blender) and blended for approximately 30 minutes. Next, magnesium stearate is added to the above mixture, and the mixture is blended continuously for approximately 1 minute.

Immediate Release Layer

20 The ranitidine hydrochloride, microcrystalline cellulose and croscarmellose sodium are added to a suitable mixer (*i.e.*, twin shell blender) and blended for approximately 30 minutes. Next, magnesium stearate is added to the above mixture, and the mixture is blended for approximately 1 minute.

25 Compression of Tablets

30 Tablets are compressed on a tablet compression machine suitable for producing layer tablets (*e.g.*, Hata press model HT-AP55-3LS supplied by Elizabeth Hata International, Inc., Banco Industrial Park, North Huntington, PA) using the procedure of *Gunsel, W. C. and Dusel, R. G., supra*, and applying pre-compression and main compression forces of approximately 0.3 and 1.5 kg, respectively.

EXAMPLE 2

35 *150 mg* Tablet, formulation with the IR:SR ration of 50:50

Ingredient	Amt/tablet
Immediate release layer	
Ranitidine HCl	84.0 mg
Microcrystalline Cellulose	78.3 mg
Croscarmellose sodium	2.5 mg
Magnesium Stearate	1.2 mg
Sustained release layer	
Ranitidine HCl	84.0 mg
Hydroxypropyl methylcellulose	300.0 mg
Lactose	129.0 mg
Magnesium Stearate	3.0 mg
TOTAL WEIGHT	682.0 mg

This tablet is prepared by the method of Example 1.

EXAMPLE 3

"300 mg" Tablet formulation with the IR:SR ratio of 40:60

5

Ingredient	Amt/tablet
Immediate release layer	
Ranitidine HCl	134.4 mg
Microcrystalline Cellulose	62.6 mg
Croscarmellose sodium	2.0 mg
Magnesium Stearate	1.0 mg
Sustained release layer	
Ranitidine HCl	201.6 mg
Hydroxypropyl methylcellulose	133.0 mg
Lactose	141.9 mg
Magnesium Stearate	3.3 mg
TOTAL WEIGHT	679.8 mg

This tablet is prepared by the method of Example 1.

10

CLAIMS

We claim:

1. A pharmaceutical solid dosage form comprising a first layer with an immediate release property and a second layer with a sustained release property, each of said layers containing ranitidine, wherein the ratio of said ranitidine in said first layer to said ranitidine in said second layer in the range of from about 30:70 to about 60:40 by weight.
- 10 2. The pharmaceutical solid dosage form of Claim 1 in the form of a laminated bilayer tablet, a concentric bilayer tablet, or a concentric layered bead.
- 15 3. A bilayer tablet comprising a first layer with an immediate release property and a second layer with a sustained release property each of said layers containing ranitidine, wherein the ratio of said ranitidine in said first layer to said ranitidine in said second layer in the range of from about 30:70 to about 60:40 by weight.
- 20 4. The bilayer tablet of Claim 3 wherein,
said first layer with an immediate release property contains
 - a) about 50 to about 200 mg of ranitidine acid addition salt, calculated as the free base
 - b) about 60 to about 90 mg of microcrystalline cellulose,
 - c) about 1 to about 5 mg of croscarmellose sodium,
 - d) about 0.5 to about 2.0 mg of magnesium stearate and
 - e) optionally one or more additional active ingredients;
- 25 and
- 30 said second layer with a sustained release property contains
 - a) about 50 to about 200 mg of ranitidine acid addition salt, calculated as the free base
 - b) about 150 to about 350 mg of hydroxypropylmethyl-cellulose,
 - c) about 100 to about 150 mg of lactose,
 - d) about 2.0 to about 4.0 mg of magnesium stearate, and
 - e) optionally one or more additional active ingredients.
- 35

5. The bilayer tablet of Claim 3, wherein total amount of said ranitidine acid addition salt is ranitidine hydrochloride in both layers and is in the range of about 100 to about 350 mg.
- 5 6. The bilayer tablet of Claim 3, wherein the ratio of said ranitidine hydrochloride in said immediate release layer to said ranitidine hydrochloride in said sustained release layer is essentially 50:50 by weight.
- 10 7. The bilayer tablet of Claim 3, wherein the ratio of said ranitidine hydrochloride in said immediate release layer to said ranitidine hydrochloride in said sustained release layer is essentially 40:60 by weight.
- 15 8. The bilayer tablet of Claim 3, wherein;
said immediate release layer contains,
 - a) 168 mg of ranitidine hydrochloride,
 - b) 78.25 mg of microcrystalline cellulose,
 - c) 2.50 mg of croscarmellose sodium, and
 - d) 1.25 mg of magnesium stearate,
- 20 and
a sustained release layer containing
 - a) 168 mg of ranitidine hydrochloride,
 - b) 300 mg of hydroxypropylmethyl-cellulose,
 - c) 129 mg of lactose,
 - d) 3.0 mg of magnesium stearate.
- 25 9. The bilayer tablet of Claim 3, wherein,
said immediate release layer contains,
 - a) 84 mg of ranitidine hydrochloride,
 - b) 78.25 mg of microcrystalline cellulose,
 - c) 2.50 mg of croscarmellose sodium, and
 - d) 1.25 mg of magnesium stearate,
- 30 and
said sustained release layer contains
 - a) 84 mg of ranitidine hydrochloride,
 - b) 300 mg of hydroxypropylmethyl-cellulose,
 - c) 129 mg of lactose,
 - d) 3.0 mg of magnesium stearate.
- 35

10. A bilayer tablet of Claim 3 wherein said sustained release layer delivers its ranitidine content over a four- to ten-hour period at a nearly constant or zero-order rate.
- 5
11. A bilayer tablet of Claim 3 wherein said sustained release layer delivers its ranitidine content over a six-hour period at a nearly constant or zero-order rate.
- 10 12. A method of treatment comprising administering to a patient in need thereof a pharmaceutical solid dosage form comprising a first layer with an immediate release property and a second layer with a sustained release property, each of said layers containing ranitidine, wherein the ratio of said ranitidine in said first layer to said ranitidine in said second layer in the range of from about 30:70 to about 60:40 by weight and the total amount of ranitidine is a pharmacologically effective amount.
- 15
13. The method of Claim 12 wherein said patient is suffering with esophagitis.

INTERNATIONAL SEARCH REPORT

International application No. PCT/US95/01928

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 9/24
US CL :424/472, 473; 514/926

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/472, 473; 514/926

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,786,503 (EDGREN ET AL) 22 November 1988, col. 7, lines 30-33; col. 9, lines 61-62; claim 25.	1-3, 5-7
Y	US, A, 4,946,685 (EDGREN ET AL) 07 August 1990, col. 3, lines 40-44; col. 12, lines 8-9; col. 15, lines 21-35.	1-3, 5-7

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means		
P document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 05 MAY 1995	Date of mailing of the international search report 24 MAY 1995
--	---

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Faximile No. (703) 305-3230

Authorized officer
JAMES M. SPEAR
JAMES M. SPEAR

Telephone No. (703) 308-2351